

REMARKS

The Office Action dated June 3, 2002, presents the examination of claims 2, 4, 6, 7, 9, and 14-23. Claims 7 and 20 are canceled. Claims 9, 14, 17, and 23 are amended. Specifically, claims 9 and 14 are amended to correct claim dependencies, and claim 23 is amended to correct a typographical error. Support for the amendment to claim 17 is found in the specification, particularly on pages 17-19. Claims 24-26 are added. Support for the addition of claims 24-26 is found in original claim 20. No new matter is inserted into the application.

Objections Maintained (Paragraphs 6-8 of the Office Action)

The Examiner notes that there are references in the specification not submitted for her consideration in an Information Disclosure Statement (IDS). Applicants point out that these references are merely background and therefore do not need disclosure to the USPTO.

The Examiner states that the drawings are acceptable only for examination purposes. Applicants acknowledge that fact and will submit the appropriate petition under 37 C.F.R. § 1.84(a)(2) or (b)(2) in order to have the color photographs accepted as formal drawings once allowable subject matter is found in the application.

Claim Objections (Paragraphs 11-12 of the Office Action)

The Examiner objects to claims 17 and 23 for containing minor typographical errors. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant objection are respectfully requested.

In response to the Examiner's remarks, Applicants amend the claims to delete the recitation of "t" in claim 17, and to insert a period mark at the end of claim 23. Thus, the instant objection is overcome.

Claim Rejection under 35 U.S.C. § 112, second paragraph (Paragraphs 13-14 of the Office Action)

The Examiner rejects claim 20 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Claim 20 is canceled, thus rendering the rejection moot. Applicants submit method claims 24-26, directed to a method for determining the progression of kidney disease, a method for prognosing the further progress of kidney disease in a patient, and a method for determining the effect of medication on kidney disease patients, respectively.

The Examiner also rejects claims 7, 9, and 17 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Claim 7 is canceled, thus rendering the rejection thereof moot. Applicants

respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that a separation step must be added to these method claims, since an antibody determines the presence of a liver-type fatty acid binding protein. In response to the Examiner's remarks, Applicants amend claim 17 to include the steps of (i) contacting the specimen with an antibody (the contacting step); (ii) removing the unbound antibody, (the separation step); and (iii) detecting the antibody complex, i.e. antibody bound with liver-type fatty acid binding protein (the detection step). Applicants respectfully submit that the claims, as amended, overcome the rejection.

Claim Rejection under 35 U.S.C. § 112, first paragraph (Paragraph 15 of the Office Action)

The Examiner rejects claims 7, 9, and 17 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. Claim 7 is canceled, thus rejection the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

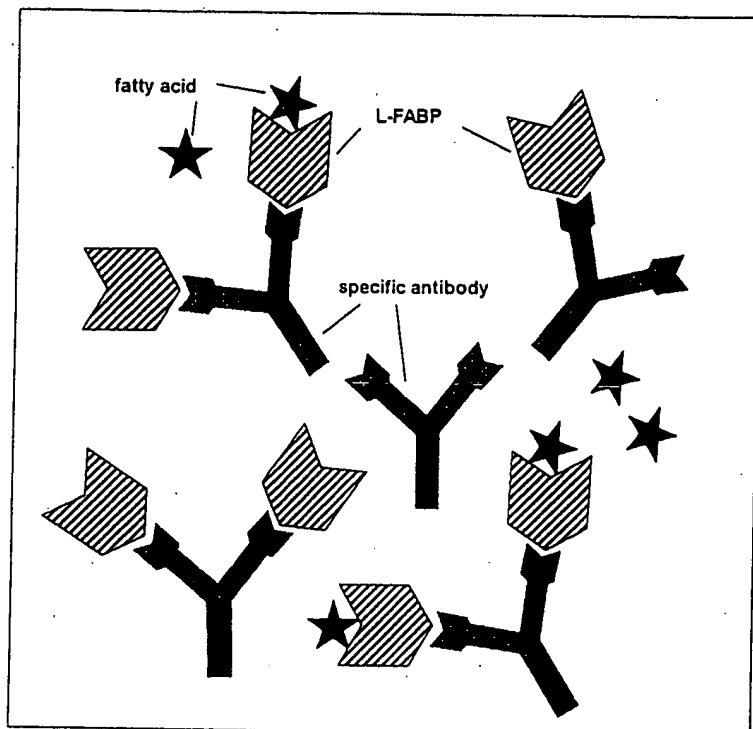
In paragraph 15 of the Office Action, the Examiner states, "If you do not have a separation step, the addition of the fatty acid will always provide a positive result regardless of the bound/unbound reagents and thus could not be utilized to detect kidney disease."

First of all, Applicants point out that the "addition of the fatty acid" is a misstatement and should correctly be "addition of the fatty acid binding protein." This misstatement may be the result of a misunderstanding of the present invention, and hence, Applicants take this opportunity to explain the present invention in order to remove any misunderstanding.

The substance to be detected by the method of the present invention is a specific protein, designated liver-type fatty acid binding protein or L-FABP, and not a fatty acid *per se*. Therefore, it is irrelevant to the method of the present invention whether the protein in the specimen is or is not in the state of binding to fatty acid, as a protein not bound to a fatty acid may also be detected by the method of the present invention. In other words, the subject to be detected by the method of the present invention includes a protein which is not bound to fatty acid.

To help explain the conventional assay using a specific antibody to the liver-type fatty acid binding protein (L-FABP), a

schematic figure of one of the embodiments showing the state of binding of an antibody to L-FABP and further to fatty acid is shown below.



The schematic figure shows that the antibody binds L-FABP whether or not L-FABP is also bound to fatty acid. Accordingly, for example, in the assay using a specific antibody to said protein, even though a fatty acid is added, it does not always provide positive results as the Examiner asserts.

Moreover, the separation step (e.g., washing) for removing unbound antibody is usually included in a conventional immunochemical assay, and hence, such a conventional step (i.e., the washing step separation of unbound antibody) is defined in the amended claim 17 in view of the Examiner's request.

Applicants respectfully submit that the claims are fully in compliance with 35 U.S.C. § 112, first paragraph. Withdrawal of the instant rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a) (Paragraph 16 of the Office Action)

I. Claims 2, 4, 6, 17-18, 20, and 22-23 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Olson et al. (*Toxicology and Applied Pharmacology*, 102:524-536, 1990) in view of Maatman et al. (*Biochem. J.* 288:285-290, 1992). Claim 20 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that it would have been obvious to use the liver-type fatty acid binding protein as taught by Maatman et al. to detect specific kidney diseases relating to FABP. Applicants respectfully disagree. The present invention is well distinguished from these references as explained below.

As defined in independent claim 16, the present invention is directed to a method for diagnosis or prognosis of a kidney disease in humans by detecting liver-type fatty acid binding protein (L-

FABP) contained in a human specimen. The present invention is also directed to a reagent or kit for the diagnosis or prognosis as defined in claim 14. The cited references do not teach or even suggest such a method for diagnosis or prognosis of kidney disease, or a reagent or kit.

(1) OLSON ET AL. AND MAATMAN ET AL. REFERENCES

Maatman et al.

It has been known that two kinds of fatty acid binding proteins (FABPs) exist in human kidneys, and the Maatman et al. reference is concerned with identification of these FABPs in human kidneys and isolation of cDNA, etc. It is disclosed therein that FABPs in human kidneys are liver-type FABP (L-FABP) and heart-type FABP (H-FABP) (cf. Maatman et al., page 285, Abstract, lines 3-4).

It is also disclosed in Maatman et al. that heart-type FABP and α_{2u} -globulin (which is also designated as "renal-type FABP") exist in rat kidneys (cf. the passages of introduction on page 285, left column, lines 20-28), wherein it is mentioned as follows:

The α_{2u} -globulin molecule is structurally not an FABP, but is more closely related to the lipocalins . . ." (cf. page 285, left column, lines 26-28).

The Maatman et al. reference further speculates as to physiological relevance of L-FABP, as follows:

We can only speculate on the physiological relevance of the two FABP types in kidneys. The liver-type FABP binds various ligands and may be involved in the renal excretion of exogenous and endogenous metabolites. The liver-type FABP also binds some drugs [2,3], and may in this way prevent nephrotoxicity." (cf. page 289, right column, lines 4-9).

Olson et al.

The Olson et al. reference is concerned with rat hyaline droplet nephropathy which is specific to male rats. It is known that in male rats, nephropathy (hyaline droplet nephropathy) is induced by administration of various hydrocarbons, where a large amount of α_{2u} -globulin (αG) is found in the droplet of kidneys. It is also disclosed that α_{2u} -globulin is specifically found in male rats, but is not found in humans. (cf. Olson et al., page 524, left column, line 1 to page 525, left column, line 37).

Olson et al. also mentions that in humans there is no risk of hydrocarbon-induced nephropathy since humans have no α_{2u} -globulin. (cf. Olson et al., page 524, Abstract, lines 2-1 from the bottom, and page 525, left column, lines 38-41).

Olson et al. also discloses the results of research on urine protein in male rats and humans (healthy men) and mentions that $\alpha 1$ -microglobulin and $\alpha 1$ -acid glycoprotein (which are analogous to α_{2u} -

globulin) were detected. (cf. page 532, right column, lines 2-6 and page 533, Table 2).

(2) THE α_{2u} -GLOBULIN IS DIFFERENT FROM L-FABP

The α_{2u} -globulin is a protein specific to male rats. Since the α_{2u} -globulin has the ability to bind to fatty acids, it may occasionally be called as a fatty acid binding protein in view of this function. However, it is known that α_{2u} -globulin belongs to a family distinguished from that of L-FABP. It is also known that the expression pattern of α_{2u} -globulin in kidneys of rats is entirely different from that of L-FABP in human kidneys. The differences between both proteins are summed up in the following table.

| | Structural distinction | Expression in kidneys |
|-----------------------------|---|---|
| Rat α_{2u} -globulin | It belongs to Lipocalin Family (which is the same family to that of α_1 -microglobulin and α_1 -acid glycoprotein, etc.). It is an extracellular protein. It is a protein specific to male rats and has never been expressed in humans. | The α_{2u} -globulin existing in rat kidneys is produced and excreted in liver and then is uptaken in kidneys. (cf. Maatman et al. page 285, left column, lines 21-29). |
| Human L-FABP | It belongs to a family different from Lipocalin Family of the α_{2u} -globulin (the same family to that of H-FABP, I-FABP, etc.) It is an intracellular protein. | It is directly produced in cells of kidneys. (cf. Maatman et al., page 286, right column, lines 4-1 from the bottom; wherein it is mentioned that the mRNA is detected in kidneys). |

(3) THERE IS NO MOTIVATION TO REPLACE α_{2u} -GLOBULIN WITH L-FABP

As is explained above, the α_{2u} -globulin is a protein specific to male rats and is clearly different from L-FABP. Both of the cited Olson et al. and Maatman et al. references never disclose nor suggest that human L-FABP is a protein corresponding to the rat α_{2u} -globulin.

Olson et al. discloses α_1 -microglobulin and α_1 -acid glycoprotein as a human protein analogous to rat α_{2u} -globulin. However, unlike L-FABP, these proteins belong to the same family of the α_{2u} -globulin (which different from the family of L-FABP). Further, Maatman et al. discloses that "the α_{2u} -globulin molecule is structurally not an FABP."

Thus, both references suggest that L-FABP has little or no relationship with α_{2u} -globulin. Accordingly, since any person skilled in the art would well understand that L-FABP has no close relationship with the α_{2u} -globulin, that skilled artisan would never be motivated to use human L-FABP in place of the rat α_{2u} -globulin in the known method for detecting the α_{2u} -globulin.

(4) THE CITED REFERENCES NEVER DISCLOSE NOR SUGGEST TO COMBINE L-FABP AND DIAGNOSIS OF KIDNEY DISEASE IN HUMANS

Maatman et al. is merely concerned with identification of FABP existing in human kidneys, but does not teach or suggest diagnosis of kidney disease. Although the Examiner points out that Maatman et al. discloses, "L-FABP binds various ligands and may be involved in the renal excretion" and further, "L-FABP binds some drugs and may in this way prevent nephrotoxicity", these are merely speculations on the part of Maatman et al. as to the physiological relevance of L-FABP. It should be noted that even though L-FABP has an activity of inhibiting nephrotoxicity of drugs, Maatman et al. does not teach or suggest the correlation between L-FABP and the diagnosis of kidney disease. Accordingly, the method of the present invention would never have been predicted from the disclosure of the cited Maatman et al. reference.

Furthermore, the rat hyaline droplet nephropathy disclosed in Olson et al. is merely known as a kidney condition specific to male rats. It is not known as a model for a clinical condition in humans. The α_{2u} -globulin protein is seen as the causal protein of kidney diseases specifically in male rats. Since the α_{2u} -globulin protein is not expressed in human kidneys, it is seen as providing absolutely no risk for nephropathy in humans. From such a disclosure in Olson et al., any person skilled in the art will rather suppose that the findings on hyaline droplet nephropathy in

male rats will rather negatively be effected on the application thereof to diagnose kidney disease in humans. Thus, Olson et al. does not give any motivation or suggest the application to diagnose kidney disease in humans.

As is clear from the above remarks, neither Olson et al. nor Maatman et al. teach or suggest the diagnosis or prognosis of kidney disease with L-FABP, and hence, that the present invention is not obvious over those cited references. Withdrawal of the instant rejection is therefore respectfully requested.

II-IV. Claims 7 and 9 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Olson et al. in view of Maatman et al., and further in view of Kimura et al. (J. Biol. Chem, 266(9):5963-5972, 1991). Claims 19 and 21 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Olson et al. in view of Maatman et al., and further in view of Galaske et al. (Pflugers Archives European Journal of Physiology, 375(3):269-277, 1978, ABSTRACT ONLY). Finally, claims 14 and 15 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Olson et al. in view of Maatman et al., and further in view of Zuk et al. (U.S. Patent 4,281,061).

Claim 7 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The present invention is well distinguished from these cited references. As is explained above, Olson et al. and Maatman et al. do not teach or suggest the method of the present invention. The remaining secondary references have no relative disclosure either as is explained below.

The Kimura et al. reference discloses that male rat kidneys contain heart-type FABP and a protein obtained by modifying α_{2u} -globulin. The Galaske et al. reference is concerned with a model for anti-GBM nephritis and discloses a method for preparing the model for nephritis. The Zuk et al. reference is concerned with an immunoassay for detecting organic materials.

Thus, those remaining references never disclose or even suggest the correlation of L-FABP and human kidney disease, and therefore do not make up for the deficiencies of Olson et al. and Maatman et al. Hence even if those references are taken into consideration together with the disclosure of the Olson et al. and Maatman et al. references, a person skilled in the art would still never predict the present invention.

Accordingly, the present invention is well distinguished from the cited references, and is well patentable over them. Withdrawal of the instant rejection is therefore respectfully requested.

Summary

Applicants respectfully submit that the above amendments and/or remarks fully address and overcome the rejections and objections of record. The instant claims are now in condition for allowance. Early and favorable action by the Examiner is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. 45,702) at the telephone number of the undersigned below.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of \$110.00 is attached hereto.

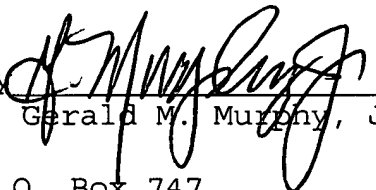
If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

Appl. No. 09/578,693

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17;
particularly, extension of time fees.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning on page 4, line 2, has been amended as follows:

Moreover, kidney-type FABP existing at male rat kidney has been known to be derived from α_{2u} -globulin, and [JP-5-33025-A] JP-5-333025-A discloses that the increase in urinary α_{2u} -globulin level can be determined in order to diagnose the α_{2u} -globulin nephropathy which is caused in male rats by the administration of chemical substances. However, it is a mere method for a specific nephropathy model, wherein α_{2u} -globulin remarkably accumulates.

In the claims:

Claims 7 and 20 are canceled.

The following claims are amended:

Claim 9. (Twice Amended) The method according to claim 16 [7], wherein the antibody specifically binding to the liver-type fatty acid binding protein is an antibody that does not cross-react with a heart muscle-type fatty acid binding protein.

Claim 14. (Twice Amended) A reagent or kit for diagnosis or prognosis, which is used in the method according to any one of claims 16, 2, 4, 6[-7], 9, and 17-26 [23].

Claim 17. (Amended) The method according to claim 16, wherein the step (b) is carried out by [an immunochemical assay using an antibody specifically binding t liver-type fatty acid binding protein and]

(i) contacting the specimen with an [said] antibody specifically binding to liver-type fatty acid binding protein;

(ii) separating unbound antibody from the antibody bound to said protein; and

(iii) detecting the antibody bound to said protein.

Claim 23. (Amended) The method according to claim 22, wherein the immune complex nephropathy is selected from the group consisting of IgA nephropathy and membranous nephropathy.

Claims 24-26 are added.